

## GUEST EDITORIAL

# A "Rose Is a Rose Is a Rose Is a Rose," But Exactly What Is a Gastric Adenocarcinoma?

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In the 14 July 1997, issue of *Lancet*, Schlemper et al. [1] reported a study in which four Japanese and four Western pathologists (from the United States, Canada, Germany, and Finland) compared their diagnoses of gastric biopsy and resection specimens having epithelial lesions ranging from reactive, through preneoplastic, to invasive carcinoma. These pathologists independently classified microscopic slides from 17 biopsies and 18 mucosal resections of 19 cases of neoplastic and nonneoplastic gastric epithelium. All of the lesions were superficial, involving only the mucosa, or when invasive, not extending beyond the submucosa, thus including examples of early gastric cancer. The selection of primarily superficial lesions focused attention on the minimal criteria required for the diagnosis of malignancy by pathologists from different parts of the world. The pattern that emerged indicated that the terminology favored by the Japanese pathologists differed from that favored by three of the Western pathologists for the same lesions; the fourth Western pathologist sided with the Japanese. Specifically, the Japanese pathologists' threshold for diagnosing carcinoma was lower than that of the Western pathologists. The Japanese did not require the presence of invasion for a diagnosis of adenocarcinoma of the stomach, whereas the Westerners did.

The authors suggest that the different diagnostic approaches brought out in this study reflect underlying differences between Japanese and Western pathologists, assuming that the participating pathologists were representative of Western and Japanese pathologists in general. Clearly, the Western group was not homogeneous, since one member broke ranks and sided with the Japanese. Therefore, we are asked to take it on faith that the opinions and use of terminology of the other three Western pathologists reflect the views of all Western pathologists, whereas the four Japanese pathologists speak for all pathologists in their country. This assumption is tenuous at best; however, for the sake of this discussion, we accept it.

Eleven of the 12 cases diagnosed by the Japanese pathologists as definite carcinoma on biopsy were also diagnosed as carcinoma on the subsequent mucosal resection by the same pathologists; the twelfth case was diagnosed as suspected carcinoma on the resection. In contrast, for the same 12 cases, the Western pathologists diagnosed definite carcinoma in only two biopsies, high-grade dysplasia with suspected carcinoma in four biopsies, high-grade dysplasia alone in three biopsies, and low-grade dysplasia in three biopsies. Definite carcinoma was diagnosed in only three of the subsequent resections, all of which were designated as either suspected or definite carcinoma on biopsy. Thus the Japanese and Western pathologists were consistent in the application of their own criteria to both biopsies and resection specimens, and the differences in diagnoses are truly the result of differences in diagnostic criteria and are not related to sample size.

Two other cases diagnosed as low-grade dysplasia on biopsy and resection by the Westerners were both diagnosed as definite carcinoma on biopsy and definite carcinoma and suspected carcinoma on resection by the Japanese, again indicating consistency among members of the two groups. However, in two additional cases that were called low-grade dysplasia by the Western pathologists, high-grade dysplasia and definite carcinoma were diagnosed by these same pathologists in the resection specimens, suggesting that Western low-grade dysplasia may be more ominous than previously suspected. The Japanese called these same two lesions definite carcinoma and adenoma with severe atypia on biopsy and

Title quotation is from Gertrude Stein, "Sacred Emily," 1913.

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definite carcinoma in both on resection. In fact, of the five cases that the Westerners called low-grade dysplasia, the Japanese diagnosed definite carcinoma in three and adenoma with severe atypia in a fourth, again indicating a much more aggressive use of the term "carcinoma" by the Japanese.

At first glance, the difference in diagnostic thresholds between these two groups would seem to be intolerable. In this age of international cooperation and data exchange, how can we in the medical community allow things to be done so differently? What are the implications of such differences in the understanding and treatment of early gastric cancer?

The results of this provocative study are appropriately viewed from two perspectives. The first is the perspective of the physician/scientist interested in the implication of these differences to the collection, evaluation, and comparison of data about gastric cancer from sites throughout the world. The other is that of the physician interested in accurately diagnosing and effectively managing patients at risk for, or already having, gastric carcinoma.

There is a perception in the West that early gastric cancers reported from Japan are invasive. For example, in a recent review of early gastric cancer in Europe the authors state that early gastric cancer can be divided into those that invade the mucosa only and those that invade the submucosa, but there is no mention of those that do not invade [2]. Clearly, these authors assumed that early gastric cancer was an invasive cancer, whether in the West or in Japan.

However, it is apparent from the Schlemper et al. study [1] that there are different criteria for the diagnosis of gastric carcinoma in Japan as compared with some Western countries. Recognition of this is critical if one attempts to compare epidemiologic, diagnostic, and therapeutic data from Japanese studies with those performed elsewhere. Western clinicians and pathologists to whom these data are important are now compelled to re-evaluate all published Japanese statistics on early gastric cancer with an eye to discriminating those that include cases in which invasion was present from those that do not. Likewise, Japanese physicians must take care in interpreting Western data. As only lesions that are invasive are capable of metastasis, it is invalid to compare studies that include noninvasive lesions with studies that include only invasive lesions.

As an example, in a recent report from Japan, 48 lesions labeled as "early gastric cancer" were treated by endoscopic resection [3]. Forty-five of these lesions were confined to the mucosa, and only three invaded the submucosa. No mention was made in the report as to how many of the 45 mucosal lesions invaded the lamina propria. Based upon the Schlemper et al. study [1], we suspect that a number of these were noninvasive lesions,

possibly a substantial number, and perhaps that accounted for the fabulous follow-up results in this report. This article was published in a British journal. When it was submitted for peer review, did the editors and reviewers realize that a number of these Japanese early gastric cancers might be diagnosed as dysplasias by British pathologists, some of whom are on the editorial board of this journal? We do not mean to imply that the treatment was inappropriate. Endoscopic mucosal resection may be a perfectly acceptable therapy for gastric epithelial dysplasia as well as for some types of early gastric cancer.

In an editorial comment accompanying the Schlemper et al. [1] study, written by two members of a Japanese surgery department, the authors did not feel that this study indicated a need for Western clinicians to alter how they interpret Japanese gastric cancer statistics [4]. Their rationale for this position is not clear. In general, the survival rates for gastric carcinoma have been superior in Japan compared to the West for comparable depths of invasion and stage. The superior Japanese survival statistics for early gastric cancer are precisely what are called into question by this study. If invasion has not been a criterion for the diagnosis of adenocarcinoma in other Japanese studies of early gastric cancer, one cannot compare outcomes with groups of patients for whom invasion was a requisite for a malignant diagnosis. Are the better survival rates for early gastric cancer in Japan genuine, or a manifestation of the inclusion of *in situ* lesions that others, particularly those in the West, would have excluded? Perhaps if noninvasive lesions are removed from the Japanese data base for early gastric cancer, the survival rates in the West might match or even surpass those in Japan.

Might these differences be minimized by insistence on standardized terminology? The World Health Organization (WHO) has published definitions for neoplasia in most body sites. In the latest version of the WHO classification of tumors of the esophagus and stomach, adenocarcinoma of the stomach is defined as "a malignant tumour of glandular epithelium composed of tubular, acinar, or papillary structures" [5]. There is no mention of invasion in this definition.

The WHO has another definition critical to this discussion, that of dysplasia, namely, "atypical changes in the epithelium considered to be precancerous." The three Western pathologists limited their designation of adenocarcinoma to neoplastic epithelium with invasion at least into the lamina propria, applying the term "dysplasia" to neoplastic epithelium that did not invade. In contrast, for the Japanese group, invasion was not a necessary criterion for the diagnosis of carcinoma, and lesions were diagnosed as carcinoma entirely *in situ*. In fact, they did not use the term "dysplasia" for any lesion, but did accept the term "adenoma." The WHO defines adenoma

as "a circumscribed benign neoplasm composed of tubular and/or villous structures lined by dysplastic epithelium." Since the definition of adenoma includes the word "dysplastic," one can assume that, in fact, the Japanese did, indeed, diagnose those lesions they called adenomas as dysplasias. Therefore, both sets of pathologists in the study, Japanese and Western, used terminology set forth in the WHO definitions. The apparent difference between the two groups is not due to use of different terminology, but a more basic difference of opinion on what is already malignant and what is precancerous. Both the Japanese and Western pathologists may adhere to the WHO definition of the word "adenocarcinoma," but they seem to be at odds as to what the word "malignant" means.

Do we need standardized nomenclature for the diagnosis of gastric mucosal neoplasia above and beyond that offered by the WHO? Standardization of nomenclature would have utility in communicating and understanding data collected in different settings. If we decide that such criteria are essential, they would have to include more specific morphologic descriptors. In the case of early gastric carcinoma, an international agreement as to the importance of invasion is requisite.

It would seem, then, that insistence on the use of standard nomenclature for histologic lesions is not enough to produce uniformity among reports. Authors of studies on early gastric cancer, as on studies of virtually any process, must state in their publications the criteria upon which their diagnoses are made. In particular, they must tell the readers whether invasion is or is not a criterion for the diagnosis of carcinoma. Only in this way will it be possible to compare Japanese and Western survival statistics for early gastric cancer.

Is the difference in diagnostic approach between pathologists in different geographic regions of concern to pathologists in any specific location in this world who are striving accurately to diagnose gastric cancerous and precancerous lesions? Perhaps the approaches preferred by the pathologists who participated in this study reflect the use of criteria appropriate to the different environments in which they live and work. The Japanese find themselves in an environment with a high incidence of gastric carcinoma, which means there is concern that the threshold established for the diagnosis of carcinoma be set at a level where a significant percentage of subsequent resections will harbor definite carcinoma, but not so high as to miss the opportunity to cure patients. They apparently have determined that threshold and are using it. This threshold may be inappropriate for those practicing in, for example, North America, where the incidence of gastric carcinoma is much lower, and (presumably) the predictive value of a noninvasive lesion for definite carcinoma would be lower.

The Japanese also find themselves in an environment

in which endoscopic mucosal resection is readily available to patients, so that the diagnosis of early gastric carcinoma usually leads to such a relatively conservative procedure. A Western pathologist who diagnoses gastric carcinoma in a gastric biopsy is likely to have a gastrectomy specimen follow. This pathologist is not going to be willing to diagnose cancer without being certain of invasion.

Is it justified to alter diagnostic terminology in order to direct appropriate therapy? Certainly, we have already chosen to tailor our diagnostic terminology to direct therapy in some sites. For example, we in the West have agreed not to diagnose carcinoma in the colon unless there is submucosal invasion, because resection is not indicated with lesions confined to the mucosa. Is it reasonable for the Japanese to do the same? The answer depends on the therapeutic implications for the diagnosis of "colonic carcinoma" in Japan. Colectomy for an intramucosal colonic neoplasm is dreadfully drastic therapy.

Would adherence to standardized nomenclature in different parts of the world improve patient care? At the moment, there are no data covering this issue, but we expect that the answer would be "probably not." It seems that Japanese and Western pathologists have successfully evolved nomenclatures that serve the needs of the patients on whose behalf the diagnosis is made.

In summary, the results of the Schlemper et al. study [1] are of concern from the standpoint of interpreting published data about early gastric cancer from pathologists in different countries, as it exposed some profound differences in diagnostic criteria. The fact that these differences were not previously recognized should alert us to examine other areas of diagnosis. Are our assumptions about the uniformity of diagnostic criteria throughout the world correct for all diseases? It is important, then, that the authors of any published report state clearly the criteria upon which their cases are chosen. However, since all peoples of the world are not the same and since the diagnosis and treatment of early gastric cancer must serve the patients, the methods of diagnosis and therapy that have evolved must be recognized as well adapted to their specific medical environments.

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